CBER Compliance Update

Current GMPs for the Pharmaceutical Industry
February 19-20, 2004
Las Vegas, Nevada

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Food and Drug Administration

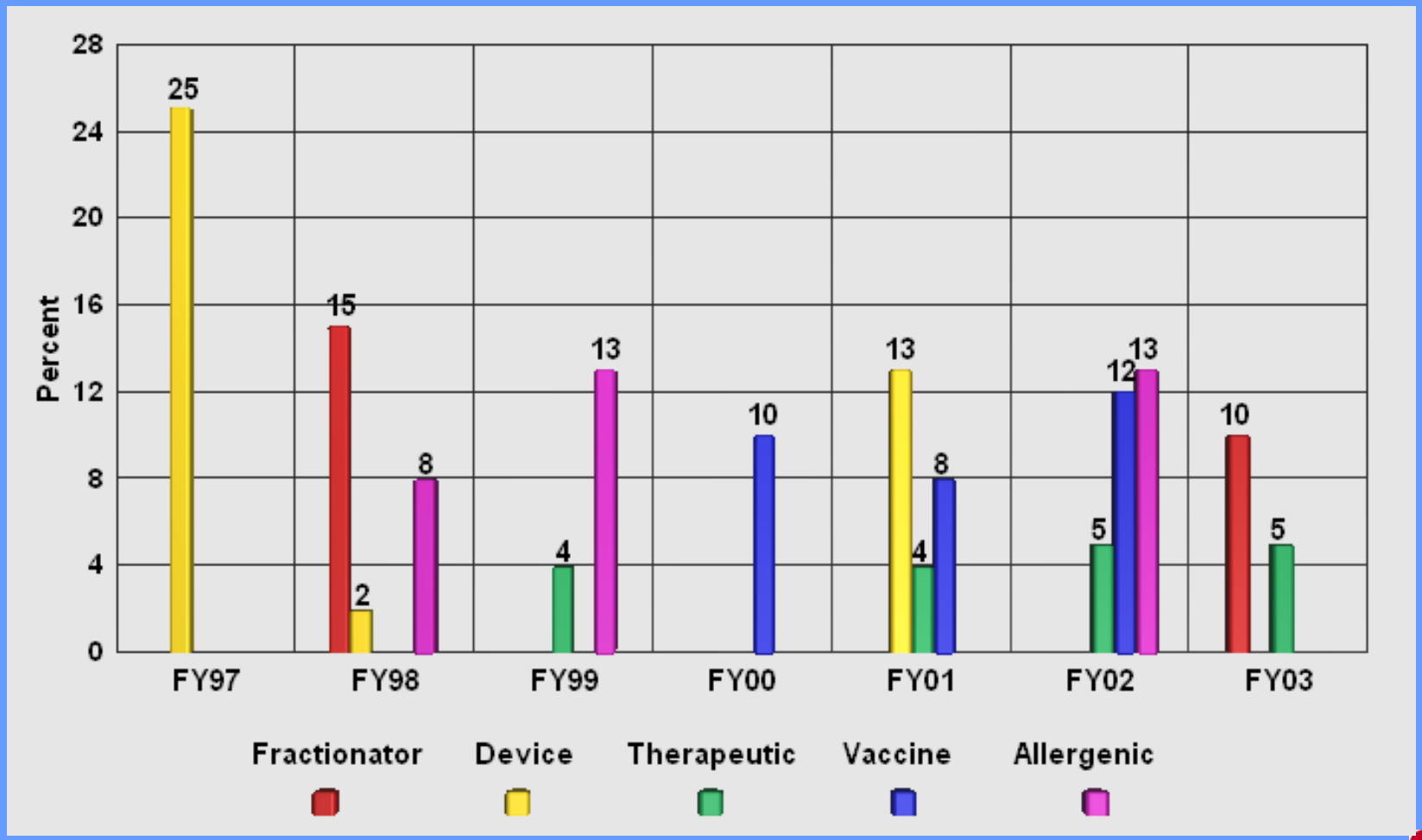
CBER Compliance Update

- Compliance Data/Actions
- Warning Letter Citations

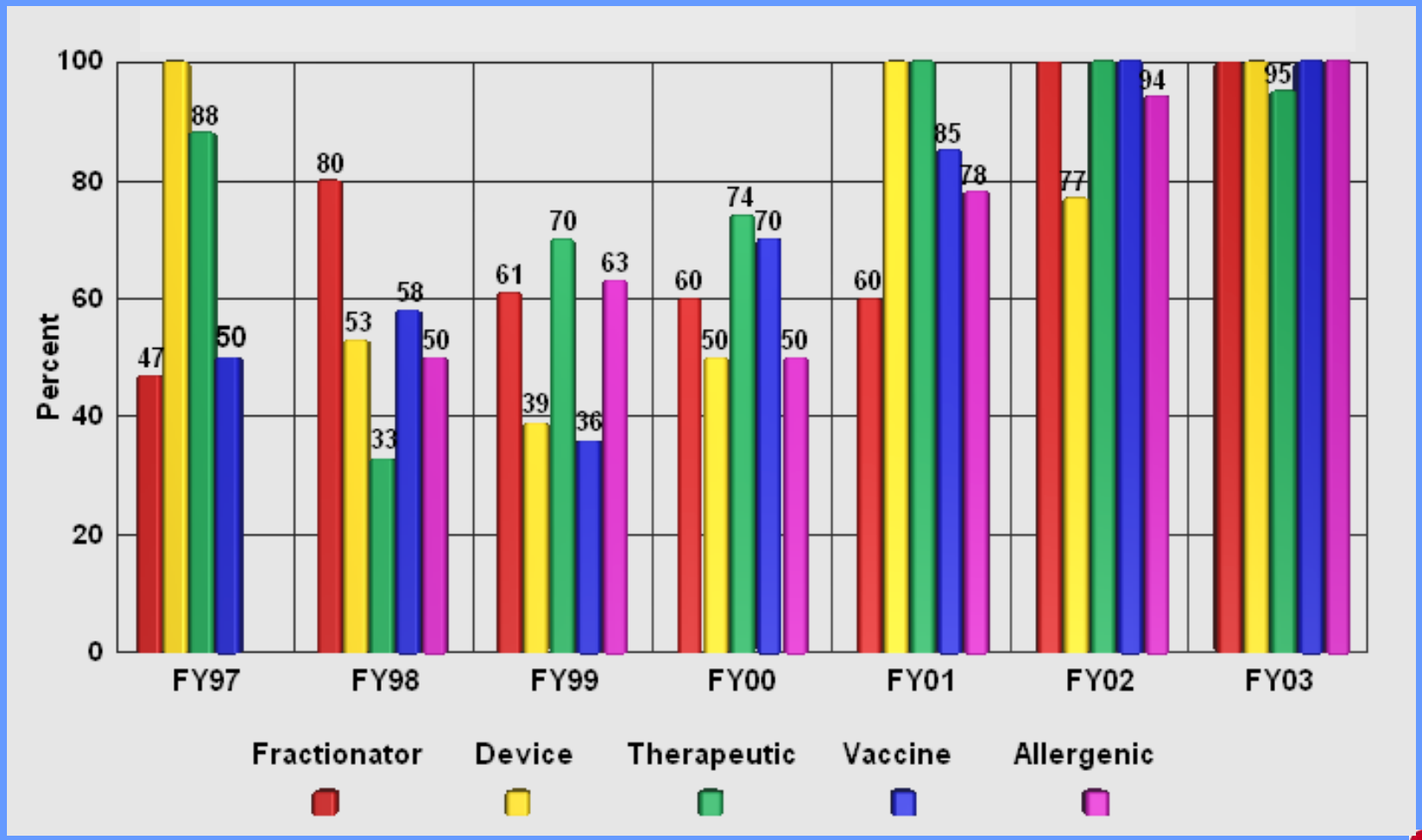
Compliance Information

- Inspection Data
- Warning Letters
- License Suspension/Revocation
- Injunction
- Seizure
- Recall

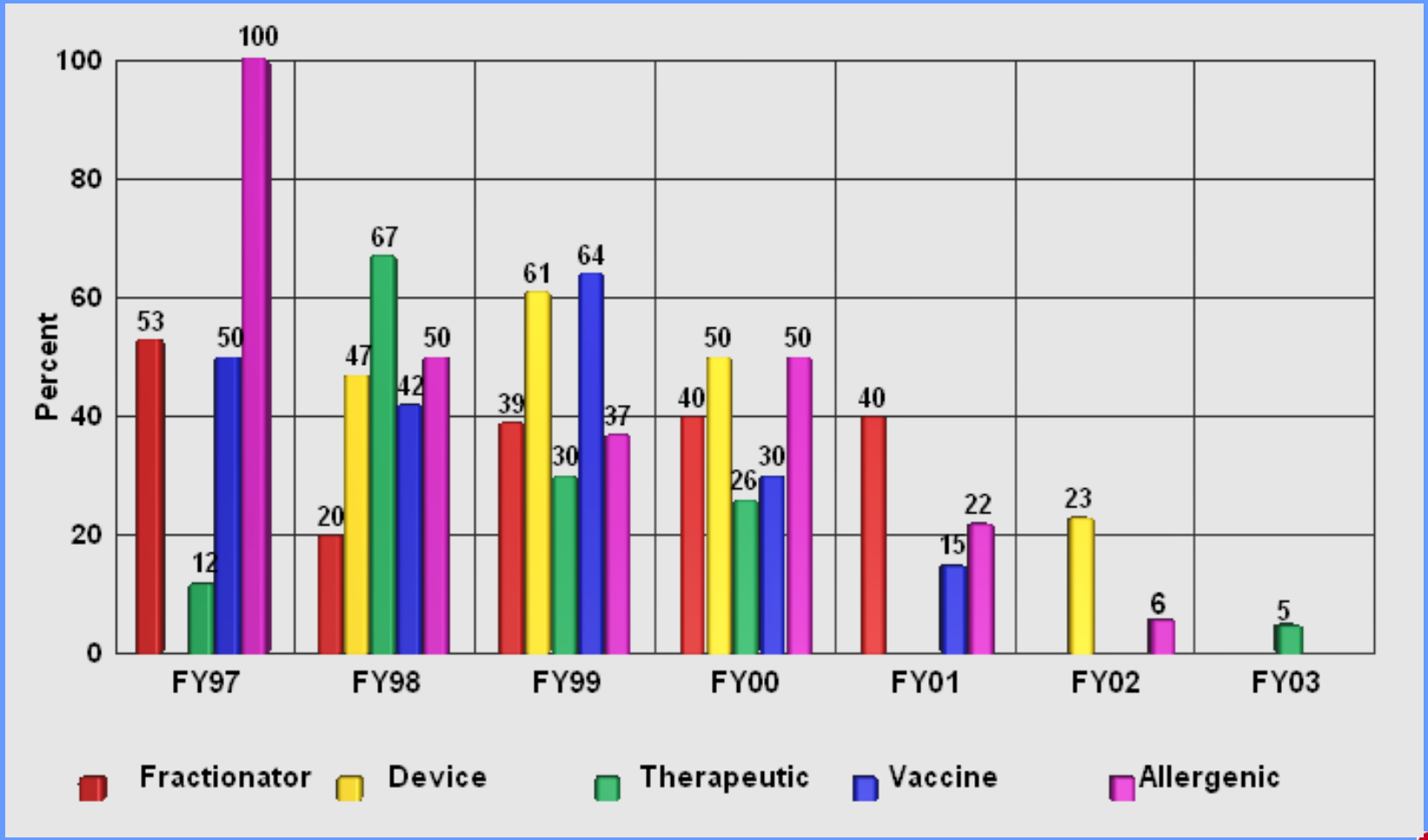
NAI Compliance Rates



NAI + VAI Compliance Rates



OAI Compliance Rates



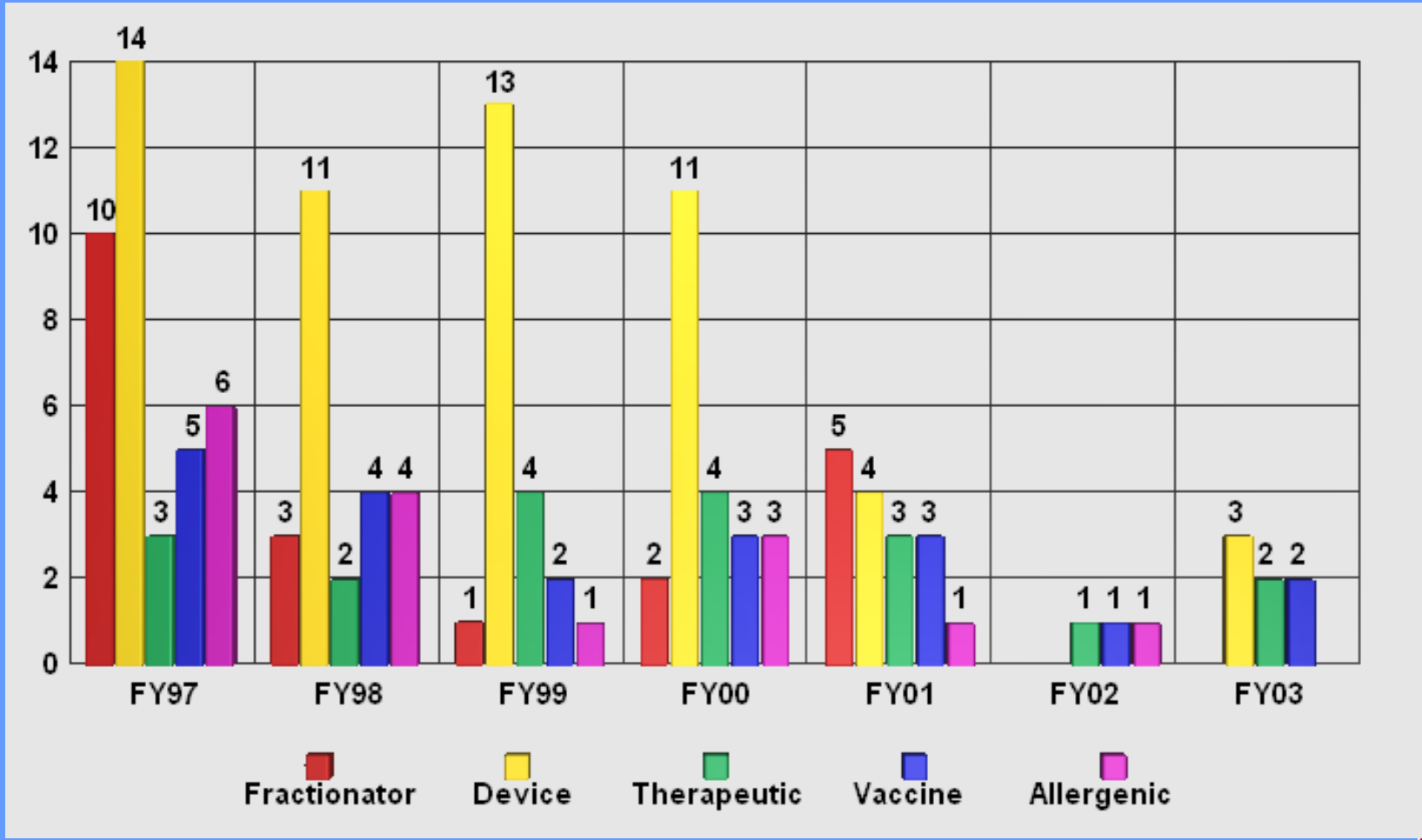
What Do These Classifications Mean?

- The classifications suggest general overall improvement, but some fluctuation remains

Warning Letters

- Deviations determined to be so significant as to warrant potential enforcement action
- Notification to manufacturer
- Prompt correction

Warning Letters



Not Limited to CGMP & Excludes BIMO

License Suspension

- 21 CFR 601.6
- Grounds for revocation exist and danger to health
- Prohibits interstate distribution
- Requires notice to selling agents and distributors with documentation of notice to CBER
- Proceed to revocation, or possibility of resolution
- May be company-wide or site specific

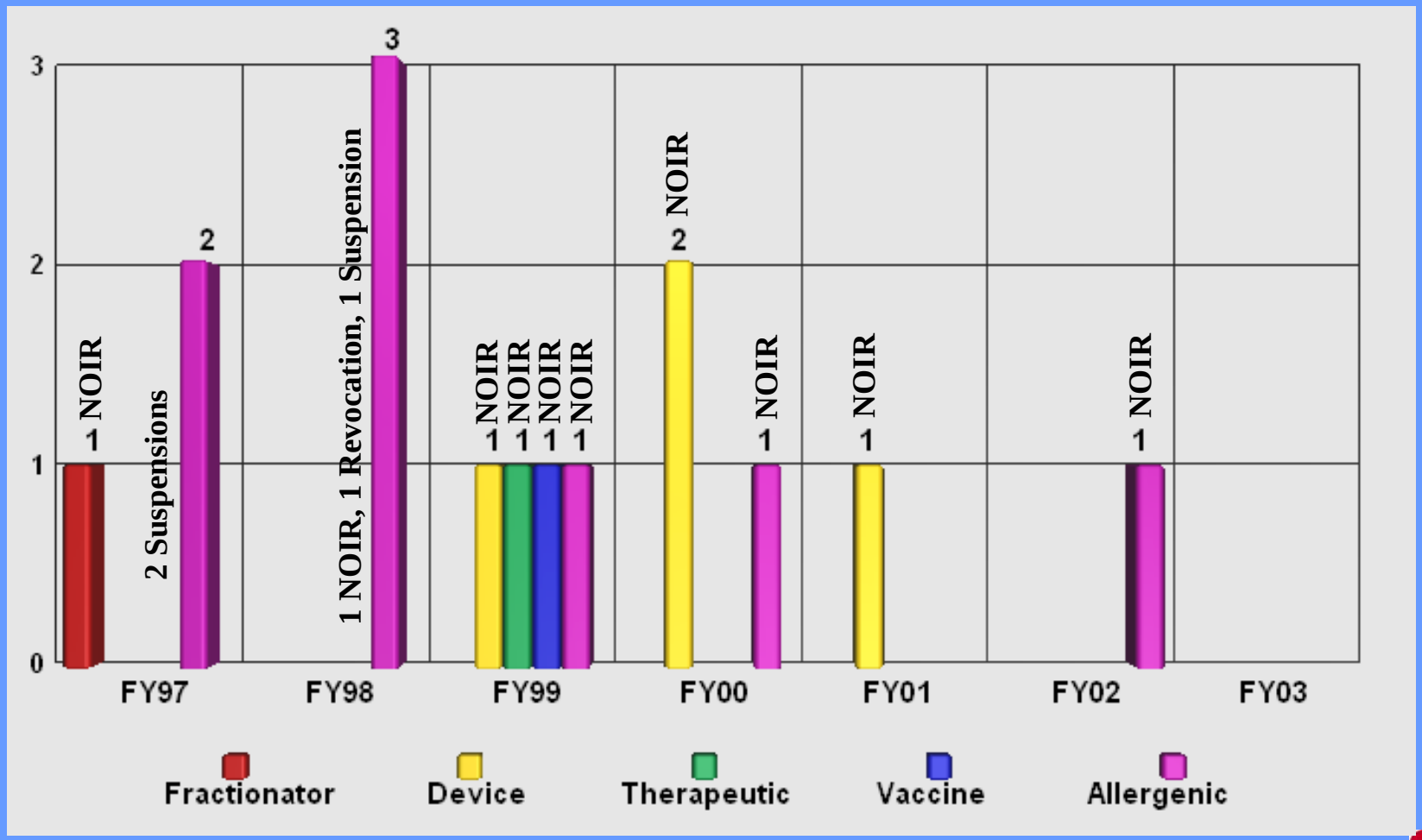
License Revocation

- 21 CFR 601.5
- Discontinuation of manufacturing
  - Manufacturer request for revocation
  - Revocation initiated by FDA
- Failure to report manufacturing change
- CGMP deficiencies
- New method of manufacturing
- Product not safe and effective for intended use(s)/misbranded
- May request hearing

Types of Revocation

- Notice of Intent to Revoke
  - Continuing, significant deficiencies
  - Prior warnings
  - Opportunity to correct and achieve compliance ("reasonable period")
  - If compliance not demonstrated, notice of opportunity for hearing (unless waived)
- Direct Revocation
  - In cases involving willfulness, FDA will proceed directly to revocation
  - No further opportunity to demonstrate compliance

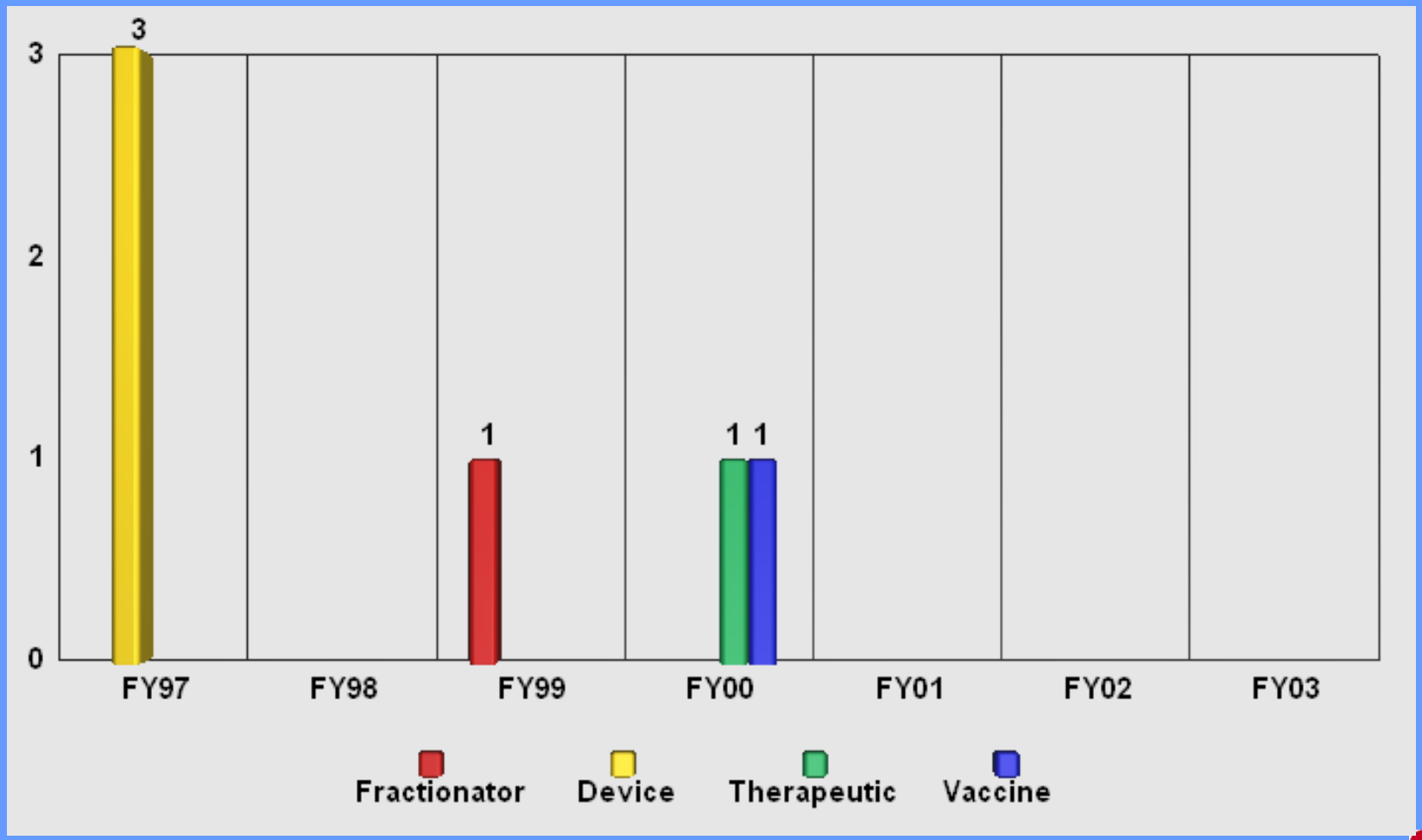
License Suspension/Revocation
Notice of Intent to Revoke



Seizures

- Removes adulterated and/or misbranded product from market
- Immediate safety concerns

Seizures


3
3
2
1
0
1
1 1
FY97
FY98
FY99
FY00
FY01
FY02
FY03
Fractionator
Device
Therapeutic
Vaccine

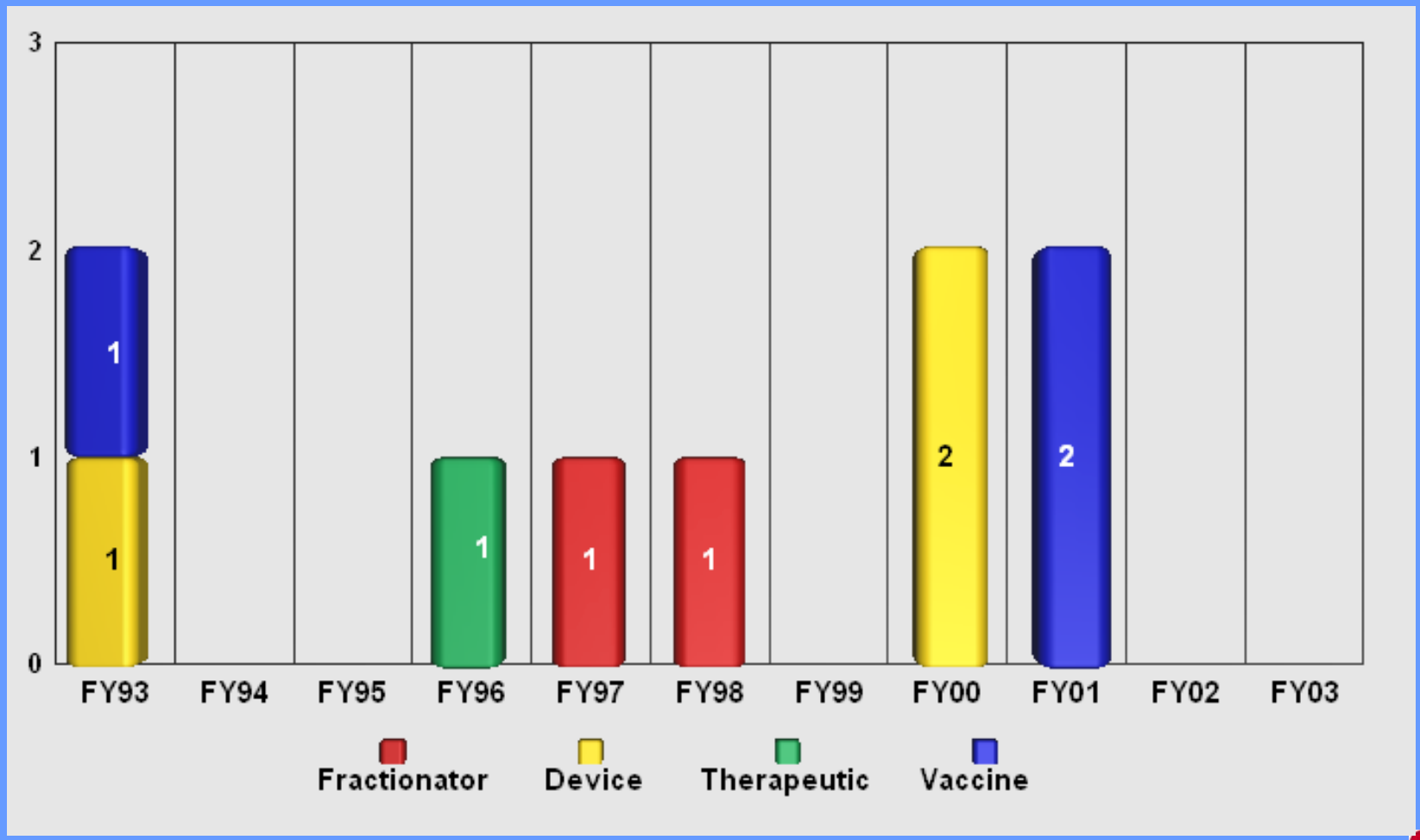
Injunction

- To stop or prevent actions that lead to violation of the law
  - e.g., manufacturing practices that may lead to the introduction of violative products into interstate commerce
- To correct the conditions that caused the violation to occur
- An order issued by the Court in which one or more defendant is ordered to do and/or refrain from doing a specified act or acts

Reasons for Injunction

- Significant out-of-compliance circumstances
  - Repeated violations
  - Types of violations (e.g., system-wide problems)
- Does not preclude additional or concurrent action
  - Recall
  - Public information
  - Seizure
  - License suspension/revocation
  - Criminal prosecution

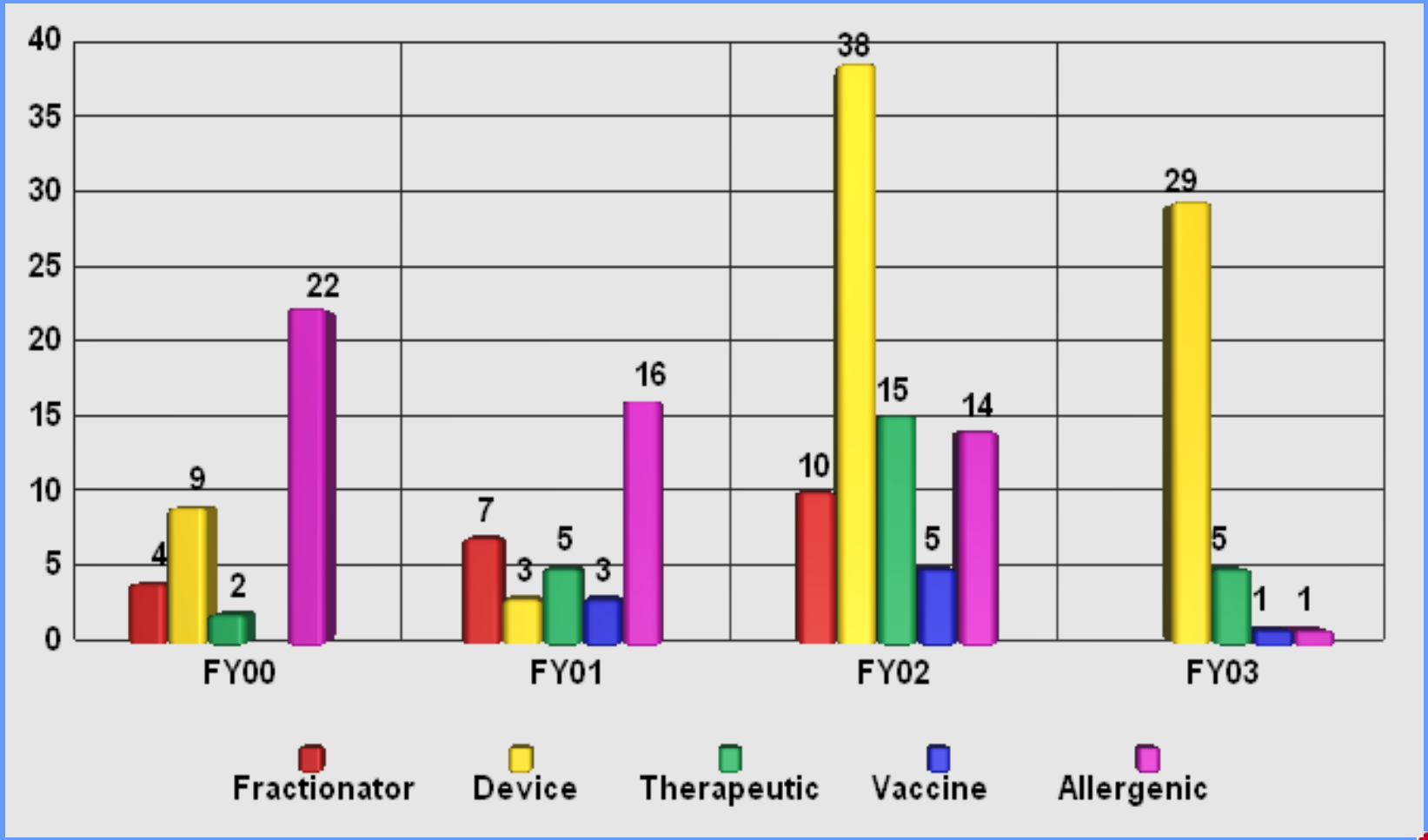
Injunctions



Recalls

- 21 CFR Part 7 Subpart C
- Voluntary action in lieu of FDA-initiated court action for product removal or correction
- Voluntary action to carry out firm's responsibility to protect the public health with respect to its products
- Classified as Class I, Class II, or Class III

Recalls Classified



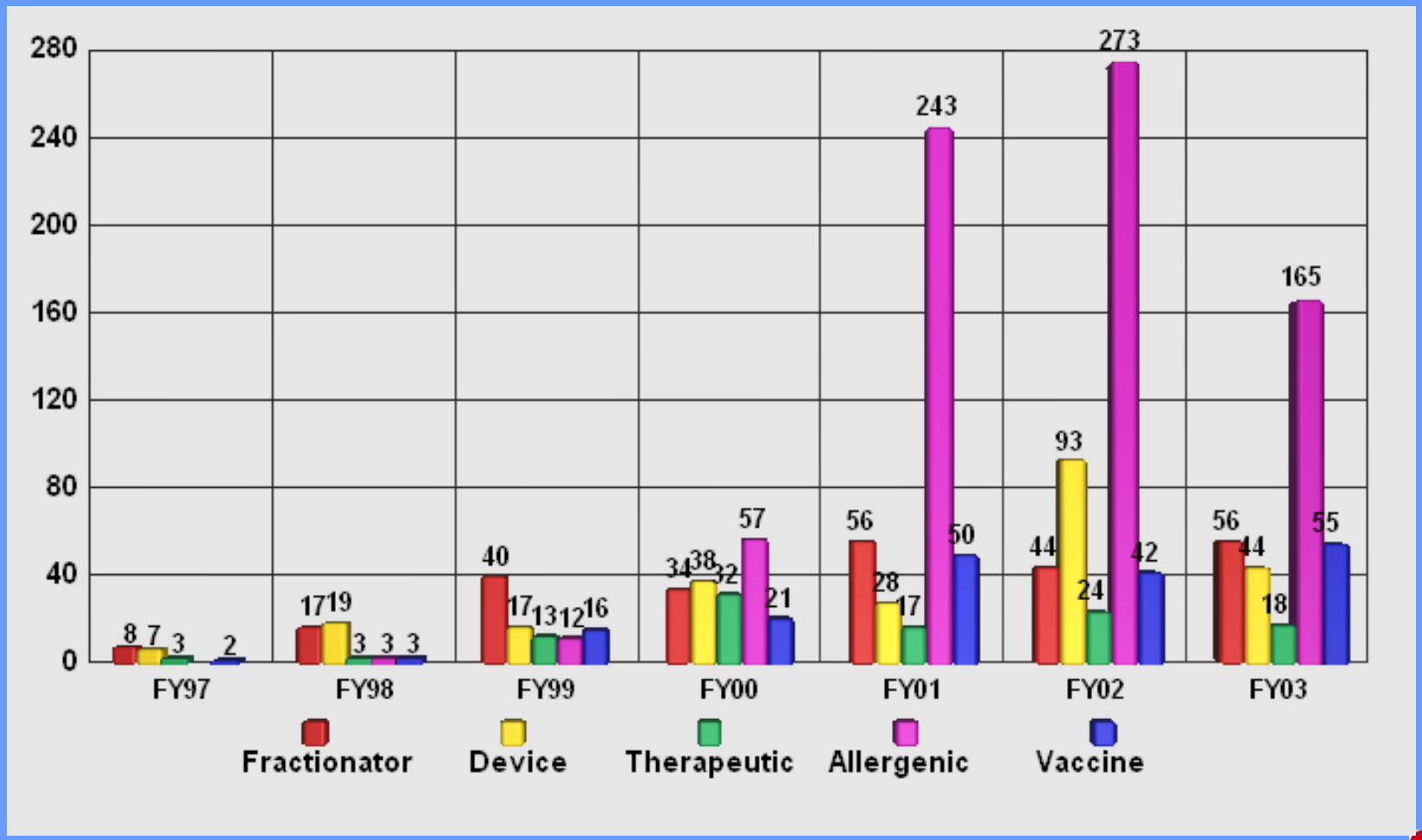
Biological Product Deviation Reports

- 21 Code of Federal Regulations Part 600.14
- Reporting of biological product deviations by licensed manufacturers
- Implemented May 7, 2001
- Established reporting time of 45 days from the date discovered

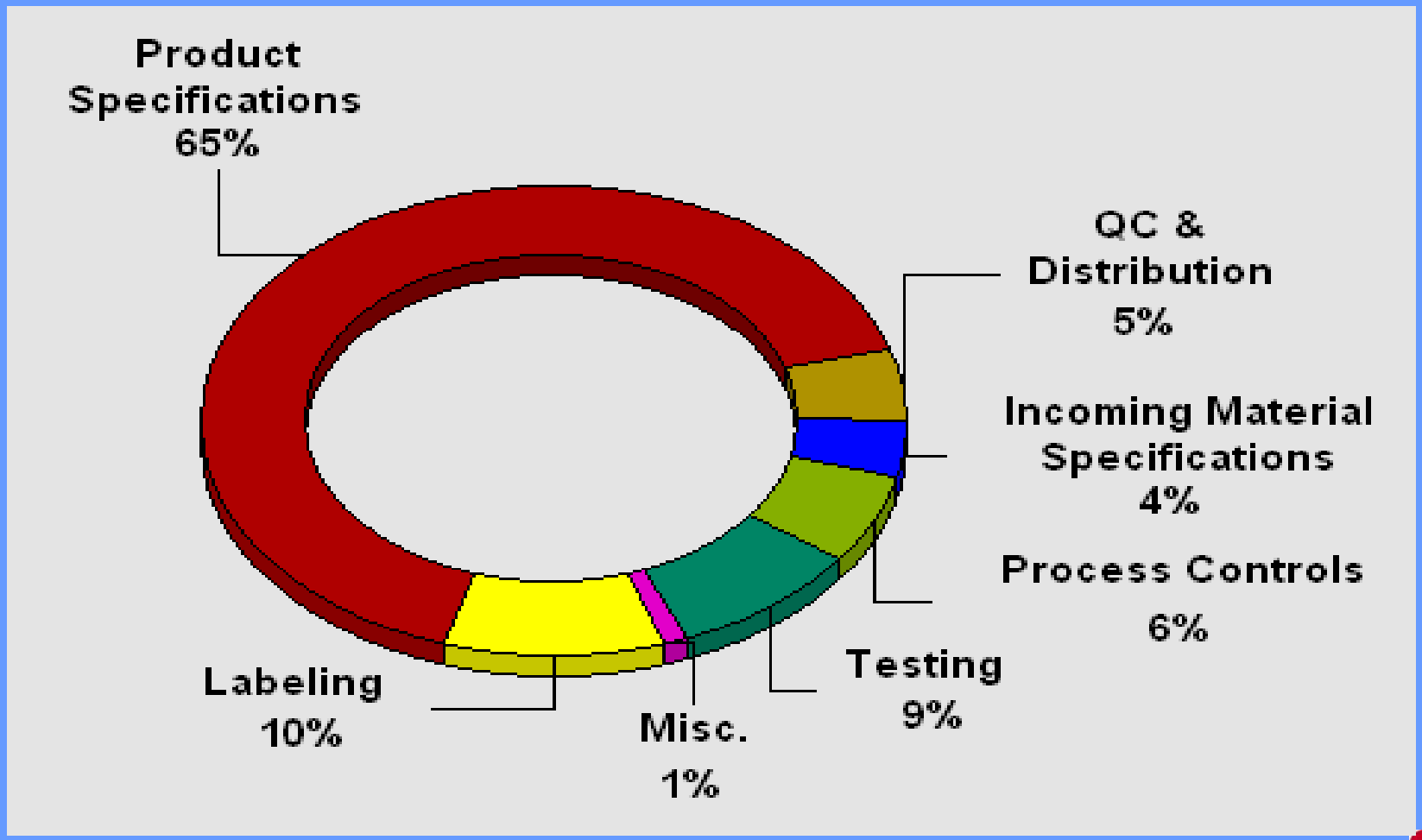
Draft BPDR Guidance

- "Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components"
  - Published 8/10/01
  - http://www.fda.gov/cber/guidelines.htm
- Final Guidance anticipated to contain revisions based on comments and additional examples

Biological Product Deviation Reports



FY03 Biological Product Deviation Reports – Non-Blood



What Do These Data Mean?

- BPDRs are increasing
  - New rule and guidance on reporting requirements ➔ more establishments reporting
  - CBER's outreach efforts (training/speeches/guidance)
  - Firms' efforts
- Recalls generally up in FY's 01 and 02, decrease in FY 03
- Increased focus on investigations as result of improved focus on deviations

Warning Letter Citations FY01-03

- Very consistent year-to-year
- May relate to failure to correct root cause

Warning Letter Citations FY01-03
continued

- Failure to implement corrective/preventive action or conduct a thorough investigation
  - 21 CFR 211.192
  - 21 CFR 820.100
- Examples
  - Repeated test failures not investigated
  - Inadequate investigation of failed particulate inspection

Warning Letter Citations FY01-03

continued

- Failure to establish and/or follow adequate written procedures
  - 21 CFR 211.100
- Examples
  - SOPs not followed
  - SOPs inadequate
  - SOPs not established

Warning Letter Citations FY01-03
continued

- Failure to properly test prior to release for distribution
  - 21 CFR 211.165
- Examples
  - Assays used in release-testing not validated
  - Retesting conducted but not addressed in SOP

Warning Letter Citations FY01-03
continued

- Failure to implement adequate production and process controls
  - 21 CFR 820.70
- Examples
  - Routine environmental monitoring not performed
  - Equipment not validated for use

Warning Letter Citations FY01-03
continued

- Failure to implement testing program to assess stability characteristics of product
  - 21 CFR 211.166(a)
- Examples
  - Stability potency tests not completed on schedule
  - Inadequate data to demonstrate sterility of components/product at end of shelf life

Information and Contacts

- www.fda.gov/cber
- Email CBER
  - Manufacturers
    - matt@cber.fda.gov
  - Consumers, health care professionals
    - octma@cber.fda.gov